UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: September 20, 2017

SUBJECT: **Chlorpropham:** Summary of Hazard and Science Policy Council (HASPOC) Meeting on May 4, 2017: Recommendations on the Need for Comparative Thyroid Assay.

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Health Effects Division (7509P)

THROUGH: Evisabel Craig, Ph.D., Co-Chair
Kelly Lowe, Co-Chair
HASPOC
Health Effects Division (7509P)

TO: Sarah S. Gallagher, Ph.D.; Biologist
Christine E. Olinger, Acting Branch Chief
Risk Assessment Branch I (RAB I)
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MEETING ATTENDEES:

HASPOC Members: Jonathan Chen, Evisabel Craig, Ray Kent, John Kough, Kelly Lowe, Elizabeth Mendez, Michael Metzger, Elissa Reaves, Kristin Rickard, Chris Schlosser, and P.V. Shah

Presenter: Sarah Gallagher

Other Attendees: Melinda Wilson, Maryanne Lewis, Yung Yang, Krystle Yozzo, Linda Taylor, Christina Swartz, Linnea Hansen, and Jordan Page.

I. PURPOSE OF MEETING

A draft human health risk assessment is currently being prepared in support of registration review for chlorpropham. The toxicological database for chlorpropham is complete; however, the database indicates that the thyroid is a target organ. Therefore, it is necessary to determine whether additional data are needed to address uncertainty related to the impact of the disruption of thyroid function during potentially sensitive lifestages (pregnancy, prenatal, and postnatal periods). The Hazard and Science Policy Council (HASPOC) met on May 4, 2017 to determine the need for additional data.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

Chlorpropham is a carbanilate herbicide and plant growth inhibitor registered for use to prevent sprouting in potatoes, to assist in the floral bud removal for Easter lilies, and to prevent fruiting in gingko trees. The pesticidal mode of action of chlorpropham is inhibition of cell division and plant tissue growth. Humans may be exposed to chlorpropham in their diet resulting from residues present on potatoes. Detectable residues were found in potato samples in field trial studies. Also, based on the registered uses, it is possible that chlorpropham might reach water resources, potentially resulting in residues in drinking water in the two counties where chlorpropham is used on Easter lilies. Residential/non-occupational handler exposure is not expected based on the registered uses; however, exposure in non-occupational settings may be expected due to spray drift from application to Easter lilies. In an occupational setting, mixers, loaders, and applicators may be exposed during application to Easter lilies and gingko trees. Post-application occupational exposures may occur following outdoor application to Easter lilies. Current personal protective equipment (PPE) on the label includes long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks. Additional PPE, including protective eyewear and a respirator is required for certain activities.

b. Toxicity Profile

The primary target organs for chlorpropham are the hematological system and the thyroid. Following subchronic and chronic oral exposures to rats, mice, and dogs, and subchronic dermal exposures to rabbits, the most consistent toxicological effect included changes in hematological parameters that were indicative of hemolytic anemia (decreased red blood cell counts, increased reticulocyte counts, increased hematopoiesis in the liver, spleen, and bone morrow, and increased hemosiderosis of the spleen). In dogs, thyroid toxicity (increased thyroid weights, histopathological changes, and decreased thyroid hormone levels) was the most sensitive effect, with dose-dependent effects on the hematopoietic system (decreased red blood cell counts, hemoglobin and hematocrit levels) observed only at a 7-fold higher dose. The dog was the most sensitive species. There was no evidence of neurotoxicity or immunotoxicity in the available studies. There was no evidence of increased quantitative or qualitative offspring susceptibility in

developmental toxicity studies in rats and rabbits or fetal susceptibility in a two-generation reproduction study in rats.

Chlorpropham has low acute oral, inhalation, and dermal toxicities (Toxicity Category III for oral and inhalation or IV for dermal exposure). Chlorpropham is a mild eye and skin irritant (Toxicity Category III and IV, respectively). It is not a dermal sensitizer.

III. STUDY WAIVER REQUESTS

a. Comparative Thyroid Assay

A number of pesticides have been shown to perturb thyroid hormone homeostasis *via* reduction of circulating thyroid hormones[1]. This perturbation may be the initial, critical effect leading to adverse effects on the developing nervous system[2,3]. When a chemical causes thyroid effects, there is inherent uncertainty about potential impacts to the developing brain in response to changing thyroid levels. There is also a lack of empirical data on whether pregnant women or the fetus are more or less susceptible, compared to adults, to the impact of chemicals that alter thyroid hormone homeostasis. This gap makes predictions on developmental susceptibility based on data from adult organisms challenging. EPA has developed guidance for conducting a comparative thyroid assay[4] that uses a mechanistic approach to generate thyroid-specific data which can address the uncertainties associated with lifestage susceptibility and allow for the establishment of PODs that would be protective of potential effects of thyroid function disruption in pregnant females on the fetus and newborn. The need for a comparative thyroid assay is based on the following considerations:

1. **Evidence for thyroid toxicity in the chlorpropham database:** In dogs, thyroid toxicity (increased thyroid weights, histopathological changes, and decreased thyroid hormone levels) was the most sensitive effect. There were no signs of thyroid toxicity in rat, rabbits, or mice.

2. **Margins of Exposure (MOE):** The size of the MOEs for combined dermal and inhalation exposure scenarios should be considered in the weight-of-evidence (WOE) analysis. For chlorpropham, combined inhalation and dermal MOEs were calculated using an oral no observed adverse effect level (NOAEL) of 5 mg/kg/day selected from the chronic toxicity study in dogs lowest observed adverse effect level (LOAEL) = 50 mg/kg based on increased thyroid weight and histopathological changes in both sexes, statistically significant decreases in thyroxine (T_4) levels seen at week 14 in males). The

[1] Hurley et al. 1998. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ. Health Perspect. 106(8): 437-445.
[2] Chan S and Kilby MD. 2000 Thyroid hormone and central nervous system development. J Endocrinol 165:1-8
[3] Fisher DA. 2000. The importance of early management in optimizing IQ in infants with congenital hypothyroidism. J Pediat 136:274-274.
[4] US EPA 2005. Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals. Washington, DC.
[5] Morreale de Escobar, G, Obregón, MJ, Escobar del Rey, F. 2004. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Practices & Research Clinical Endocrinology & Metabolism, Volume 18, Issue 2: 225-248.

level of concern (LOC) for all exposure scenarios was 1000, which incorporates 10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X database uncertainty factor. Assuming label-directed PPE (long sleeved shirt, long pants, socks plus shoes, chemical resistant gloves, respirators in some cases), total (dermal + inhalation) occupational handler MOEs ranged from 18-18,000. Post-application occupational dermal risk estimates range from 3.7 to 78 on the day of application to Easter lilies. For spray drift following application to Easter lilies, adult dermal MOEs at the field edge range from 65 to 370 depending on the application method and the spray type/nozzle configuration. Children 1 to < 2 year old combined dermal and incidental oral MOEs at the field edge range from 32 to 180 depending on the use site/application method and the spray type/nozzle configuration.

3. **Chronic Population-Adjusted Doses:** To evaluate chronic dietary exposures, the chronic population-adjusted dose (cPAD) is 0.05 mg/kg/day based on the NOAEL of 5 mg/kg/day from the chronic toxicity study in dogs and a 100-fold uncertainty factor (10X for interspecies extrapolation; 10X for intraspecies variation; 1X for Food Quality Protection Act Safety Factor). A chronic aggregate dietary (food + drinking water) risk assessment was conducted for chlorpropham using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16 which incorporates consumption data from the USDA NHANES/WWEIA; 2003-2008. The chronic analysis assumed anticipated residues (ARs) from USDA Pesticide Data Program (PDP) monitoring data, and 100% CT for all registered commodities. Processing factors, calculated based on previously submitted residue data, were used for some potato commodities. The highest chronic exposure estimate was for the population subgroup all infants (children 1-2 years old year old), which utilized 16% of the cPAD for chlorpropham.

IV. HASPOC CONCLUSIONS

Based on a WOE approach, the HASPOC concludes that, while there is uncertainty regarding potential developmental susceptibility to thyroid function disruption, a comparative thyroid assay in rats (comparing pregnant animals, fetuses, postnatal animals, and adult animals) is not required for chlorpropham at this time. However, an *in vitro* comparative metabolism study is needed to further characterize differences among dog, rodent, and humans. This approach considered all of the available hazard and exposure information including: (1) the thyroid gland is a target organ for dogs; (2) the current PODs selected for risk assessment are based on thyroid effects in dogs; (3) there is uncertainty about potential lifestage susceptibility; (4) using the current PODs, risk estimates were below the HASPOC margin of safety target for chlorpropham. The decision to not require a rat CTA is based on the observation that there were no treatment-related effects on the thyroid in rats up to the limit dose and no quantitative or qualitative offspring or fetal susceptibility in the developmental or two-generation reproduction studies in rats. In contrast, thyroid effects were observed in dogs at a dose of 50 mg/kg/day. Typically, the rat is the most sensitive species for thyroid effects; however, for chlorpropham the dog is uniquely sensitive in the absence of thyroid effects in the rat. To address the uncertainty associated with lifestage susceptibility, the

HASPOC will not be requesting a dog CTA study. Instead, the HASPOC is requesting that the Registrant conduct an *in vitro* comparative metabolism study that would evaluate the metabolites and metabolic rates for dogs, rats, and humans to help elucidate the basis for the species differences in target organ toxicity. Until these data are submitted, a 10X uncertainty factor will be applied to all short-term, intermediate-term, and chronic exposure scenarios. The HASPOC recommends the registrant discuss this study and its design with HED prior to conducting the study.